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Date: 11-26-03

Signature:

(Michael Boyd)

Docket No.: 140942000310
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Joseph A. HEDRICK et al

Application No.: 09/770,528

Group Art Unit: 1646

Filed: January 25, 2001

Examiner: E. Kemmerer

For: MAMMALIAN CYTOKINES; RELATED
REAGENTS AND METHODS

APPELLANTS' BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellants file this Appeal Brief, pursuant to 37 C.F.R. § 1.192, from the final rejection in the Office Action, mailed August 12, 2003, and from the Advisory Action, mailed October 29, 2003. A Notice of Appeal is mailed herewith. Accordingly, this Appeal Brief is timely filed.

Appellants respectfully request that the rejection be reversed. In accordance with 37 C.F.R. § 1.192, this Brief is filed in triplicate and is accompanied by the required fee. Also included is an Appendix of the Claims on Appeal, attached as Exhibit A.

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I. REAL PARTY IN INTEREST

The real party in interest in this Appeal is the assignee, Schering Corporation. Appellant's assignment to Schering Corporation was recorded at Reel 9623 and Frame 0945 on December 9, 1998, for the parent application, Serial No. 09/130,972.

II. RELATED APPEALS AND INTERFERENCES

There are no other Appeals or Interferences known to Appellants, Appellants' undersigned attorney, or assignee that will directly affect, or be directly affected by, or have a bearing on, the decision by the Board of Patent Appeals and Interferences in the presently pending appeal.

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The claims on appeal are claims 7-9 and 20-25.

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The present specification relates to the novel cytokine, IL-1 δ , and the specific invention set forth in the instant application relates to compounds that bind IL-1 δ . More specifically, the present invention relates to a binding compound comprising an antigen binding site from an antibody, which specifically binds to a mature polypeptide comprising at least 8 contiguous amino acid residues from IL-1 δ (*i.e.*, SEQ ID NO:2) wherein the antigen binding site specifically binds an epitope located within the contiguous amino acid residues, as well as kits and methods related to such binding compounds.

The specification discloses IL-1 δ as a member of the IL-1 family of cytokines. The specification first discloses IL-1 δ as a cytokine defined by a disclosed amino acid sequence, SEQ ID NO:2. *See* specification at page 17, Table 1, and at page 31, lines 13-14. Analysis of the DNA sequence, amino acid sequence, and protein structure reveals that IL-1 δ is a member of the IL-1 family of cytokines. *See* specification at page 22, Table 3; at page 23, figure at bottom of page; and at page 40, lines 18-26 and lines 31-35.

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at page 31, lines 10-13, the specification states that “IL-1 δ ... protein will have a number of different biological activities, *e.g.*, in the immune system, and will include inflammatory functions or other innate immunity responses.” At page 31, lines 33-35, the specification discloses that “IL-1 δ and IL-1 ϵ ... should have related activities, typically affecting similar immune functions, including inflammatory responses.” At page 78, line 34 to page 79, line 12, the specification discloses a therapeutic utility for IL-1 δ and its binding compounds that includes abnormal expression of the cytokine that “will typically be manifested by immunological disorders.” The specification also discloses that IL-1 δ , like the related family member IL-1 γ , may be involved in viral infections. *See* specification, at page 79, lines 7-12. Finally, the specification discloses IL-1 δ as “likely to play a role in modulating local and systemic inflammatory responses.” *See* specification at page 79, lines 26-28.

VI. ISSUES

Issue 1: Whether the specification sets forth a specific, substantial, and credible utility under 35 U.S.C. § 101 and 112, first paragraph, for the invention of Claims 7-9 and 20-25.

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Issue 1: The specification identifies a specific, substantial, and credible utility for the claimed invention of Claims 7-9 and 20-25.

Appellants have asserted a specific, substantial, and credible utility for a binding compound specific for IL-1 δ

Claims 7-9 and 20-25 have been rejected as lacking either a credible, specific, and substantial utility or a well-established utility. According to the Office, a lack of disclosed utility for IL-1 δ results in a lack of utility for a binding compound specific for IL-1 δ . The Examiner asserted in the most recent Final Action that while inflammation is a specific response and Debets *et al.* provides detailed information about IL-1 δ expression, the specification as originally filed only indicates that IL-1 δ “plays a role” in inflammation. *See* Paper No. 20, page 3. The Examiner argued that the specification fails to provide the specific information disclosed in Debets *et al.*, *i.e.*, that IL-1 δ is upregulated in psoriasis. *Id.* The Examiner also asserted that the literature does not support the specification’s more specific assertions of the effects of IL-1 δ , *e.g.*, induction of chemoattractants, enhancement and promotion of adherence of adhesion molecules resulting in the recruitment of macrophages/neutrophils, and induction of fibroblast growth. *Id.* In the Advisory Action, the Examiner maintained the utility rejection because a diverse array of compounds and environmental stimuli “play a role” in inflammation including lye, a scratch, aspirin, and ice. *See* Paper No. 21, page 2. The Examiner again argued that the upregulation of IL-1 δ is not psoriasis is not disclosed and therefore the utility standard is not met. *Id.* Appellant asserts that this rejection is in error.

Legal standard of the utility requirement

In rejecting the presently claimed invention, the Office has apparently taken the position that only certain evidence substantiated by actual experimental data would establish patentable utilities. However, such is not the legal standard for the utility requirement.

First, a disclosed utility for the claimed subject matter satisfies the utility requirement under § 101 absent evidence which would cast doubt on the objective truth of the disclosed utility. *Manual of Patent Examination Procedure* (hereinafter “M.P.E.P.”) § 2107.02 (III)(A) (8th ed.

2001). There is no legal requirement that the disclosed utility must be supported by conclusive experimental data. According to the M.P.E.P.,

[a]s a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

MPEP § 2107.02 (III) (A), at page 2100-39 (emphasis original).

Second, an applicant is not required to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt” or “as a matter of statistical certainty.” *See* M.P.E.P. § 2107.02 (VII). An applicant is only required to provide evidence if, when considered as a whole, leads the skilled artisan to conclude that the asserted utility is more likely than not true. *See* M.P.E.P. § 2107.03 (II). Furthermore, for inventions with pharmaceutical or therapeutic utilities, a reasonable correlation between the evidence and the asserted utility is sufficient. In fact, the courts “have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmaceutical utility as being supportive of an assertion of therapeutic utility for a new compound.” *See* M.P.E.P. § 2107.03 (II) (emphasis added).

Third, an applicant is required to make only one credible assertion of specific utility for the claimed invention to satisfy the utility requirement of 35 U.S.C. §§ 101 and 112. *See* M.P.E.P. § 2107.02 (1), at page 2100-37. Appellants note that additional statements of utility, even if not credible, do not render the claimed invention lacking in utility. *Id.*

Finally, the determination of credibility of an asserted utility is “whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided.” *See* M.P.E.P. § 2107.02 (III) (B). An assertion of utility is credible unless the logic underlying the assertion is seriously flawed or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. *Id.*

Appellants respectfully submit that the Office appears to have adopted an incorrect standard in maintaining the instant rejection. Specifically, the Office appears to be requiring a certain and exact evidence be disclosed for IL-1δ if the specification is to meet the utility requirement of §§ 101 and 112, *i.e.*, that the specification state that IL-1δ is upregulated in psoriasis. In essence, the Office

is requiring proof beyond a reasonable doubt regarding the role of IL-1 δ in inflammation and immune responses.

The instant specification discloses at least one specific, substantial and credible utility that satisfies the requirement of §§ 101 and 112. First, the specification discloses at least one specific utility for IL-1 δ in inflammation based on structural homology to the IL-1 family and supported by the evidence of record. Second, the asserted utility of IL-1 δ in inflammation is a real world or substantial use. Third, the practical utility of IL-1 δ is believable to a person of ordinary skill, and thus is a credible utility.

IL-1 δ has a specific utility

The specification discloses a utility for IL-1 δ as a cytokine with a role in inflammation that is sufficiently specific to satisfy the utility requirement under 35 U.S.C. § 101 and 112. Inflammation is not a general term for a diverse set of diseases. Rather, it describes a complex, but predictable, response that includes defined cytokines (*e.g.*, IL-1, TNF- α), cellular components (*e.g.*, neutrophils, lymphocytes), and other soluble mediators (*e.g.*, platelets) that interact to induce vascular permeability, cellular extravasation into tissue, and activation of the tissue-recruited cells. *See* Exhibits A and B, submitted with Amendment Under 37 C.F.R. § 116, dated February 3, 2003 (Paper No. 16). The diversity of the resulting disease states is specific to the organ system in which the inflammation occurs, not the initiating inflammatory process. The cascade of events described as “inflammation” is defined and well known as a biological process with common characteristics regardless of the organ system in which inflammation occurs. Therefore, the identification of inflammation as a specific pathological process in which IL-1 δ plays a role is a specific assertion of utility for IL-1 δ .

Appellants are not required to predict the specific effects of IL-1 δ in inflammation as asserted by the Office as there is no predetermined amount or character of evidence needed to support an asserted utility. Because the threshold of utility is not high under 35 U.S.C. § 101, an invention is useful if it is merely capable of providing some identifiable benefit. *Juicy Whip, Inc. v.*

Orange Bang, Inc., 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). In other words, only a minimal utility is required. Therefore, the character and amount of evidence required is determined by what is claimed and whether it contravenes established scientific principle and belief. The character and amount of evidence disclosed in the specification is sufficient to meet the minimal utility standard set forth in 35 U.S.C. § 101 for the reasons discussed below.

First, the specification discloses the novel cytokine, IL-1 δ and assert a specific biological activity for IL-1 δ as a modulator of at least one specific disease condition: inflammation. *See, e.g.*, the specification, at page 31, lines 33-35 and at page 79, line 26 to page 80, line 11. In the instant application, Appellants claim compounds that bind IL-1 δ comprising an antigen binding site, *e.g.*, an antibody.

The character or substance of the evidence supporting this utility lies in the structural and sequence similarities between IL-1 δ and other family members. *See* specification at page 22, Table 3, at page 23, figure at bottom of page, and at page 40, lines 18-26 and lines 31-35. The members of the IL-1 family all possess a common β -barrel structure. IL-1 δ has this common β -barrel structure. To date, all of the IL-1 family members that have been functionally characterized are involved in inflammation. Thus, the specification discloses that IL-1 δ affects inflammatory responses. *See* specification, at page 31, lines 33-35.

Evidence submitted by Appellants supports this utility. First, Appellants made the post-filing reference of Debets *et al.*, *J. Immunol.*, 167: 1440 (2001) of record in the Response to Office Action dated September 12, 2002 (Paper No. 12). Debets *et al.* first demonstrates a role for IL-1 δ in inflammation using an *in vitro* assay recognized by the skilled artisan to represent the inflammatory cascade in the skin. Specifically, Debets *et al.* shows the induction of IL-1 δ expression in keratinocytes after stimulation by the classical pro-inflammatory cytokines of IL-1 β and TNF- α . *See* Debets *et al.*, at 1442-44, Figures 3 and 6. Debets *et al.* then confirm the results of the *in vitro*

assay using *in vivo* analysis of clinical samples. Specifically, Debets *et al.* analyze skin samples known to represent an inflammatory condition in the skin, *i.e.*, psoriasis, for the induction of IL-1 δ . Debets *et al.* demonstrate that IL-1 δ is overexpressed in the psoriatic skin lesions. See Debets, at pages 1443-44 and Figure 6. Thus, Debets *et al.* provides evidence of the role of IL-1 δ in inflammation using *in vitro* and *in vivo* assays that are recognized in the art as indicative of inflammation and inflammatory responses.

Second, the submission of Kumar *et al.*, *J. Biol. Chem.*, 275: 10308-14 (2000) (also made of record in Paper No. 12) provides further evidence of a specific utility for IL-1 δ in the modulation of immune functions, particularly inflammation, when viewed in light of Debets *et al.* Debets *et al.* specifically identify at least one mechanism by which IL-1 δ modulates an inflammatory response, *i.e.*, the inhibition of IL-1 ϵ binding to its receptor. See Debets *et al.*, at page 1443. Kumar *et al.* establish IL-1 ϵ is expressed *in vivo* in an art-recognized murine model of skin inflammation (*i.e.*, chronic oxazolone-mediated contact hypersensitivity). See Kumar, at page 10312-13 and Figure 5. Thus, the combined findings of Kumar *et al.* and Debets *et al.* support a specific utility for IL-1 δ as a modulator of inflammation through its ability to act as an antagonist of IL-1 ϵ .

This utility does not contravene established scientific principle and belief. First, the post-filing publications provide additional evidence of the specific utility for IL-1 δ as disclosed in the specification. In fact, the documented biological activity of IL-1 δ is exactly as disclosed in the instant specification, *i.e.*, as a modulator of inflammation. Second, the role of IL-1 family members in inflammation is well-known and, therefore, the disclosed utility for IL-1 δ does not contradict any established scientific principle and belief. In point of fact, the disclosed utility supplements and supports the scientific beliefs about the IL-1 family and its role in inflammation.

Appellants respectfully submit that the diverse compounds that are alleged to elicit an inflammatory response are not relevant to the specific utility of IL-1 δ in inflammation. More specifically, lye, a scratch, aspirin, and ice are not comparable to IL-1 δ . At a minimum, the

exemplary agents listed by the Examiner in the Advisory Action of October 29, 2003 (Paper No. 20) require no specific biological interaction to mediate any of their alleged effects in inflammation, do not play identified roles in inflammation-mediated disease states, *e.g.*, psoriasis, and are not elicited in some cell types, *e.g.*, keratinocytes, but not in others, when treated with pro-inflammatory cytokines, *e.g.*, IL-1 β and TNF- α . Moreover, the Examiner has provided no objective evidence that the skilled artisan considers such agents as lye, a scratch, aspirin, or ice comparable to a cytokine, particularly a cytokine in a well-characterized family. In other words, such a comparison is tantamount to comparing apples and oranges, a comparison that would be incredible to one of ordinary skill in the art. Thus, such a comparison is irrelevant and serves only to muddy the waters where the instant disclosure and objective evidence of record overwhelmingly demonstrate at least one well-established utility for IL-1 δ .

Finally, Appellants disagree with the Office's assertion that the literature does not support the specification's more specific assertions of the effects of IL-1 δ . The list of effects cited by the Examiner represents a limited laundry list of the characteristics of inflammatory responses. The literature submitted by Appellants do not examine these characteristics. Nonetheless, the evidence of record is sufficiently probative regarding the expression of IL-1 δ during inflammatory responses and diseases and the modulation of the binding of IL-1 ϵ to establish the specific utility of IL-1 δ .

IL-1 δ has a substantial utility

The assertion of a utility for IL-1 δ in inflammation satisfies the substantiality prong for the utility requirement under §§ 101 and 112. According to the M.P.E.P., "courts have repeatedly found that the mere identification of a pharmacological activity of a compound is relevant to an asserted pharmacological use provides an 'an immediate benefit to the public' and satisfies the utility requirement." § 2107.01 (III) (emphasis original). Likewise, the identification of IL-1 δ as having a role in inflammation and as an inhibitor of the activity of IL-1 ϵ provides researchers and physicians with a new target for intervention in inflammatory responses and diseases. For example,

an antibody that binds IL-1 δ has a “real world” use because the ability to measure the presence of IL-1 δ in inflammation permits the diagnosis of inflammation and the identification of potential pharmacologic agents for preventive measures or monitoring of disease progression. Therefore, the utility disclosed for IL-1 δ and its binding antibodies is substantial.

IL-1 δ has a credible utility

IL-1 δ 's utility in inflammation is credible to one of skill in the art in view of the disclosure and the post-filing publications of record. Appellants respectfully submit that “credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions.” *See* M.P.E.P. § 2107 (II) (B)(ii). First, inflammation is considered a specific disease process by the skilled artisan, and therefore, it would be credible to the skilled artisan that a new cytokine's participation in inflammation represents a utility. Second, the instant specification specifically discloses a utility for IL-1 δ as a modulator of inflammation. *See* remarks above. Third, the skilled artisan would recognize that similar structural motifs correlate with similar biological functions within certain families. The IL-1 family of proteins is one such family. The role of IL-1 in inflammation was well-established at the time of filing the instant application. *See, e.g.,* J.C. Fantone, *et al., Inflammation, in* PATHOLOGY (E. Rubin and J.L. Farber 1988) at page 59 (made of record in Paper No. 16 as Exhibit B). Fourth, the *in vitro* and *in vivo* data submitted in post-filing publications support the utility for IL-1 δ disclosed by Appellants and further convey the usefulness of IL-1 δ . In sum, the combination of the shared structural motifs and the biologic data credibly conveys to the skilled artisan a specific and substantial utility for IL-1 δ in inflammation.

The specification discloses additional utilities for IL-1 δ

The specification also sets forth other specific, substantial, and credible utilities for IL-1 δ . Namely, the specification discloses IL-1 δ 's utility as a cytokine involved in viral infections and immunological disorders. *See* specification at page 78, line 33 to page 79, line 12. The post-filing

references of record provide support for these specific, substantial, and credible utilities. First, Debets *et al.* demonstrates that IL-1 δ acts as a specific and potent antagonist of IL-1 ϵ . See Debets, at page 1443. Thus, one of ordinary skill in the art would appreciate that as an antagonist of an IL-1 family member, IL-1 δ has utility in modulating the immune response mediated by IL-1 ϵ . The specification discloses that IL-1 ϵ and IL-1 δ have related activities in immune functions. See specification, at page 31, lines 33-35. In this case, IL-1 ϵ and IL-1 δ regulate a single signaling cascade as agonist and antagonist, respectively. Second, Kumar *et al.* establishes IL-1 ϵ is expressed *in vivo* in response to a viral infection (*i.e.*, herpes simplex virus). See Kumar, at page 10312-13 and Figures 4 and 5. In other words, IL-1 ϵ functions similarly to other characterized IL-1 family members, namely IL-1 α and IL-1 β , in its involvement in viral response, while IL-1 δ functions similarly to other characterized IL-1 family members, namely IL-1 α , as a modulator of a particular IL-1 family member's function, *i.e.*, IL-1 ϵ . Therefore, these references support an additional, disclosed utility for IL-1 δ as a modulator of immune responses, particularly in anti-viral infections.

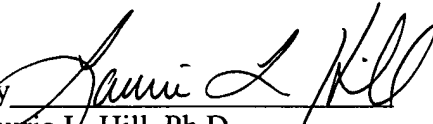
Taken together, the specification discloses IL-1 δ as having a specific, substantial, and credible utility in inflammation, viral infections, and immune responses in general. Therefore, the utility requirement under §§ 101 and 112 has been met. Appellants respectfully submit that the rejections under 35 U.S.C. §§ 101 and 112, first paragraph, are overcome and request the passage of the pending claims to allowance.

IX. CLAIMS INVOLVED IN THE APPEAL

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

Dated: November 26, 2003

Respectfully submitted,

By 
Laurie L. Hill, Ph.D.

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APPENDIX A**Claims Involved in the Appeal of Application Serial No. 09/770,528**

Claims 1-6 (Canceled)

Claim 7 (Previously presented): A binding compound comprising an antigen binding site from an antibody, which specifically binds to a mature polypeptide comprising at least 8 contiguous amino acid residues from SEQ ID NO:2, wherein said antigen binding site specifically binds an epitope located within said contiguous amino acid residues.

Claim 8 (Previously presented): The binding compound of Claim 7, wherein said binding compound is an Fv, Fab, or Fab2 fragment.

Claim 9 (Original): A kit comprising said binding compound of Claim 7, and:

- a) a compartment comprising said binding compound; and/or
- b) instructions for use or disposal of reagents in said kit.

Claims 10-19 (Canceled)

Claim 20 (Previously presented): A method of:

A) making an antiserum comprising an antibody of Claim 7, comprising immunizing a mammal with an immunogenic amount of a peptide comprising a 12 consecutive amino acid segment of SEQ ID NO:2; thereby causing said antiserum to be produced; or

B) producing an antigen:antibody complex, comprising contacting a rodent IL-1 δ protein or peptide with a binding compound of Claim 7; thereby allowing said complex to form.

Claim 21 (Original): The binding compound of Claim 7, wherein said antibody is a polyclonal antibody.

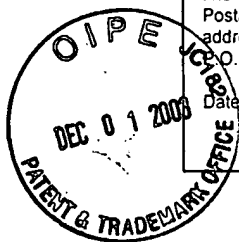
Claim 22 (Original): The binding compound of Claim 7, wherein said antibody is detectably labeled.

Claim 23 (Original): The binding compound of claim 7, wherein said at least 8 contiguous amino acid residues of SEQ ID NO:2 is selected from the group consisting of residues 8-24; 27-48; 56-73; 77-106; 108-125; 130-156; and 74-98.

Claim 24 (Original): The binding compound of claim 7, wherein said polypeptide comprises at least 12 contiguous amino acid residues from SEQ ID NO:2.

Claim 25 (Previously presented): The binding compound of claim 24, wherein said 12 consecutive amino acid segment is selected from:

- (1) LeuCysPheArgMetLysAspSerAlaLeuLysValLeuTyrLeuHisAsn-Asn;
- (2) IleSerValValProAsnArgAlaLeuAspAlaSerLeuSerProValIle-LeuGlyValGln;
- (3) SerProValIleLeuGlyValGlnGlyGlySerGlnCys;
- (4) ProIleLeuLysLeuFluProValAsnIleMetFluLeu;
- (5) ThrSerSerPheGluSerAlaAlaTyrProGlyTrpPhe;
- (6) PheLeuCysThrSerProLguAlaAspGlnProVal; or
- (7) ThrGlnIleProGluAspProAlaTrpAspAlaProlle.



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Signature: [Signature]

(Michael Boyd)

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Legal standard of the utility requirement

In rejecting the presently claimed invention, the Office has apparently taken the position that only certain evidence substantiated by actual experimental data would establish patentable utilities. However, such is not the legal standard for the utility requirement.

First, a disclosed utility for the claimed subject matter satisfies the utility requirement under § 101 absent evidence which would cast doubt on the objective truth of the disclosed utility. . *Manual of Patent Examination Procedure* (hereinafter “M.P.E.P.”) § 2107.02 (III)(A) (8th ed.

2001). There is no legal requirement that the disclosed utility must be supported by conclusive experimental data. According to the M.P.E.P.,

[a]s a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

MPEP § 2107.02 (III) (A), at page 2100-39 (emphasis original).

Second, an applicant is not required to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt” or “as a matter of statistical certainty.” *See* M.P.E.P. § 2107.02 (VII). An applicant is only required to provide evidence if, when considered as a whole, leads the skilled artisan to conclude that the asserted utility is more likely than not true. *See* M.P.E.P. § 2107.03 (II). Furthermore, for inventions with pharmaceutical or therapeutic utilities, a reasonable correlation between the evidence and the asserted utility is sufficient. In fact, the courts “have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmaceutical utility as being supportive of an assertion of therapeutic utility for a new compound.” *See* M.P.E.P. § 2107.03 (II) (emphasis added).

Third, an applicant is required to make only one credible assertion of specific utility for the claimed invention to satisfy the utility requirement of 35 U.S.C. §§ 101 and 112. *See* M.P.E.P. § 2107.02 (1), at page 2100-37. Appellants note that additional statements of utility, even if not credible, do not render the claimed invention lacking in utility. *Id.*

Finally, the determination of credibility of an asserted utility is “whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided.” *See* M.P.E.P. § 2107.02 (III) (B). An assertion of utility is credible unless the logic underlying the assertion is seriously flawed or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. *Id.*

Appellants respectfully submit that the Office appears to have adopted an incorrect standard in maintaining the instant rejection. Specifically, the Office appears to be requiring a certain and exact evidence be disclosed for IL-1δ if the specification is to meet the utility requirement of §§ 101 and 112, *i.e.*, that the specification state that IL-1δ is upregulated in psoriasis. In essence, the Office

is requiring proof beyond a reasonable doubt regarding the role of IL-1 δ in inflammation and immune responses.

The instant specification discloses at least one specific, substantial and credible utility that satisfies the requirement of §§ 101 and 112. First, the specification discloses at least one specific utility for IL-1 δ in inflammation based on structural homology to the IL-1 family and supported by the evidence of record. Second, the asserted utility of IL-1 δ in inflammation is a real world or substantial use. Third, the practical utility of IL-1 δ is believable to a person of ordinary skill, and thus is a credible utility.

IL-1 δ has a specific utility

The specification discloses a utility for IL-1 δ as a cytokine with a role in inflammation that is sufficiently specific to satisfy the utility requirement under 35 U.S.C. § 101 and 112. Inflammation is not a general term for a diverse set of diseases. Rather, it describes a complex, but predictable, response that includes defined cytokines (*e.g.*, IL-1, TNF- α), cellular components (*e.g.*, neutrophils, lymphocytes), and other soluble mediators (*e.g.*, platelets) that interact to induce vascular permeability, cellular extravasation into tissue, and activation of the tissue-recruited cells. *See* Exhibits A and B, submitted with Amendment Under 37 C.F.R. § 116, dated February 3, 2003 (Paper No. 16). The diversity of the resulting disease states is specific to the organ system in which the inflammation occurs, not the initiating inflammatory process. The cascade of events described as “inflammation” is defined and well known as a biological process with common characteristics regardless of the organ system in which inflammation occurs. Therefore, the identification of inflammation as a specific pathological process in which IL-1 δ plays a role is a specific assertion of utility for IL-1 δ .

Appellants are not required to predict the specific effects of IL-1 δ in inflammation as asserted by the Office as there is no predetermined amount or character of evidence needed to support an asserted utility. Because the threshold of utility is not high under 35 U.S.C. § 101, an invention is useful if it is merely capable of providing some identifiable benefit. *Juicy Whip, Inc. v.*

Orange Bang, Inc., 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). In other words, only a minimal utility is required. Therefore, the character and amount of evidence required is determined by what is claimed and whether it contravenes established scientific principle and belief. The character and amount of evidence disclosed in the specification is sufficient to meet the minimal utility standard set forth in 35 U.S.C. § 101 for the reasons discussed below.

First, the specification discloses the novel cytokine, IL-1 δ and assert a specific biological activity for IL-1 δ as a modulator of at least one specific disease condition: inflammation. *See, e.g.*, the specification, at page 31, lines 33-35 and at page 79, line 26 to page 80, line 11. In the instant application, Appellants claim compounds that bind IL-1 δ comprising an antigen binding site, *e.g.*, an antibody.

The character or substance of the evidence supporting this utility lies in the structural and sequence similarities between IL-1 δ and other family members. *See* specification at page 22, Table 3, at page 23, figure at bottom of page, and at page 40, lines 18-26 and lines 31-35. The members of the IL-1 family all possess a common β -barrel structure. IL-1 δ has this common β -barrel structure. To date, all of the IL-1 family members that have been functionally characterized are involved in inflammation. Thus, the specification discloses that IL-1 δ affects inflammatory responses. *See* specification, at page 31, lines 33-35.

Evidence submitted by Appellants supports this utility. First, Appellants made the post-filing reference of Debets *et al.*, *J. Immunol.*, 167: 1440 (2001) of record in the Response to Office Action dated September 12, 2002 (Paper No. 12). Debets *et al.* first demonstrates a role for IL-1 δ in inflammation using an *in vitro* assay recognized by the skilled artisan to represent the inflammatory cascade in the skin. Specifically, Debets *et al.* shows the induction of IL-1 δ expression in keratinocytes after stimulation by the classical pro-inflammatory cytokines of IL-1 β and TNF- α . *See* Debets *et al.*, at 1442-44, Figures 3 and 6. Debets *et al.* then confirm the results of the *in vitro*

assay using *in vivo* analysis of clinical samples. Specifically, Debets *et al.* analyze skin samples known to represent an inflammatory condition in the skin, *i.e.*, psoriasis, for the induction of IL-1 δ . Debets *et al.* demonstrate that IL-1 δ is overexpressed in the psoriatic skin lesions. See Debets, at pages 1443-44 and Figure 6. Thus, Debets *et al.* provides evidence of the role of IL-1 δ in inflammation using *in vitro* and *in vivo* assays that are recognized in the art as indicative of inflammation and inflammatory responses.

Second, the submission of Kumar *et al.*, *J. Biol. Chem.*, 275: 10308-14 (2000) (also made of record in Paper No. 12) provides further evidence of a specific utility for IL-1 δ in the modulation of immune functions, particularly inflammation, when viewed in light of Debets *et al.* Debets *et al.* specifically identify at least one mechanism by which IL-1 δ modulates an inflammatory response, *i.e.*, the inhibition of IL-1 ϵ binding to its receptor. See Debets *et al.*, at page 1443. Kumar *et al.* establish IL-1 ϵ is expressed *in vivo* in an art-recognized murine model of skin inflammation (*i.e.*, chronic oxazolone-mediated contact hypersensitivity). See Kumar, at page 10312-13 and Figure 5. Thus, the combined findings of Kumar *et al.* and Debets *et al.* support a specific utility for IL-1 δ as a modulator of inflammation through its ability to act as an antagonist of IL-1 ϵ .

This utility does not contravene established scientific principle and belief. First, the post-filing publications provide additional evidence of the specific utility for IL-1 δ as disclosed in the specification. In fact, the documented biological activity of IL-1 δ is exactly as disclosed in the instant specification, *i.e.*, as a modulator of inflammation. Second, the role of IL-1 family members in inflammation is well-known and, therefore, the disclosed utility for IL-1 δ does not contradict any established scientific principle and belief. In point of fact, the disclosed utility supplements and supports the scientific beliefs about the IL-1 family and its role in inflammation.

Appellants respectfully submit that the diverse compounds that are alleged to elicit an inflammatory response are not relevant to the specific utility of IL-1 δ in inflammation. More specifically, lye, a scratch, aspirin, and ice are not comparable to IL-1 δ . At a minimum, the

exemplary agents listed by the Examiner in the Advisory Action of October 29, 2003 (Paper No. 20) require no specific biological interaction to mediate any of their alleged effects in inflammation, do not play identified roles in inflammation-mediated disease states, *e.g.*, psoriasis, and are not elicited in some cell types, *e.g.*, keratinocytes, but not in others, when treated with pro-inflammatory cytokines, *e.g.*, IL-1 β and TNF- α . Moreover, the Examiner has provided no objective evidence that the skilled artisan considers such agents as lye, a scratch, aspirin, or ice comparable to a cytokine, particularly a cytokine in a well-characterized family. In other words, such a comparison is tantamount to comparing apples and oranges, a comparison that would be incredible to one of ordinary skill in the art. Thus, such a comparison is irrelevant and serves only to muddy the waters where the instant disclosure and objective evidence of record overwhelmingly demonstrate at least one well-established utility for IL-1 δ .

Finally, Appellants disagree with the Office's assertion that the literature does not support the specification's more specific assertions of the effects of IL-1 δ . The list of effects cited by the Examiner represents a limited laundry list of the characteristics of inflammatory responses. The literature submitted by Appellants do not examine these characteristics. Nonetheless, the evidence of record is sufficiently probative regarding the expression of IL-1 δ during inflammatory responses and diseases and the modulation of the binding of IL-1 ϵ to establish the specific utility of IL-1 δ .

IL-1 δ has a substantial utility

The assertion of a utility for IL-1 δ in inflammation satisfies the substantiality prong for the utility requirement under §§ 101 and 112. According to the M.P.E.P., "courts have repeatedly found that the mere identification of a pharmacological activity of a compound is relevant to an asserted pharmacological use provides an 'an immediate benefit to the public' and satisfies the utility requirement." § 2107.01 (III) (emphasis original). Likewise, the identification of IL-1 δ as having a role in inflammation and as an inhibitor of the activity of IL-1 ϵ provides researchers and physicians with a new target for intervention in inflammatory responses and diseases. For example,

an antibody that binds IL-1 δ has a “real world” use because the ability to measure the presence of IL-1 δ in inflammation permits the diagnosis of inflammation and the identification of potential pharmacologic agents for preventive measures or monitoring of disease progression. Therefore, the utility disclosed for IL-1 δ and its binding antibodies is substantial.

IL-1 δ has a credible utility

IL-1 δ 's utility in inflammation is credible to one of skill in the art in view of the disclosure and the post-filing publications of record. Appellants respectfully submit that “credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions.” *See* M.P.E.P. § 2107 (II) (B)(ii). First, inflammation is considered a specific disease process by the skilled artisan, and therefore, it would be credible to the skilled artisan that a new cytokine's participation in inflammation represents a utility. Second, the instant specification specifically discloses a utility for IL-1 δ as a modulator of inflammation. *See* remarks above. Third, the skilled artisan would recognize that similar structural motifs correlate with similar biological functions within certain families. The IL-1 family of proteins is one such family. The role of IL-1 in inflammation was well-established at the time of filing the instant application. *See, e.g.,* J.C. Fantone, *et al., Inflammation, in* PATHOLOGY (E. Rubin and J.L. Farber 1988) at page 59 (made of record in Paper No. 16 as Exhibit B). Fourth, the *in vitro* and *in vivo* data submitted in post-filing publications support the utility for IL-1 δ disclosed by Appellants and further convey the usefulness of IL-1 δ . In sum, the combination of the shared structural motifs and the biologic data credibly conveys to the skilled artisan a specific and substantial utility for IL-1 δ in inflammation.

The specification discloses additional utilities for IL-1 δ

The specification also sets forth other specific, substantial, and credible utilities for IL-1 δ . Namely, the specification discloses IL-1 δ 's utility as a cytokine involved in viral infections and immunological disorders. *See* specification at page 78, line 33 to page 79, line 12. The post-filing

references of record provide support for these specific, substantial, and credible utilities. First, Debets *et al.* demonstrates that IL-1 δ acts as a specific and potent antagonist of IL-1 ϵ . See Debets, at page 1443. Thus, one of ordinary skill in the art would appreciate that as an antagonist of an IL-1 family member, IL-1 δ has utility in modulating the immune response mediated by IL-1 ϵ . The specification discloses that IL-1 ϵ and IL-1 δ have related activities in immune functions. See specification, at page 31, lines 33-35. In this case, IL-1 ϵ and IL-1 δ regulate a single signaling cascade as agonist and antagonist, respectively. Second, Kumar *et al.* establishes IL-1 ϵ is expressed *in vivo* in response to a viral infection (*i.e.*, herpes simplex virus). See Kumar, at page 10312-13 and Figures 4 and 5. In other words, IL-1 ϵ functions similarly to other characterized IL-1 family members, namely IL-1 α and IL-1 β , in its involvement in viral response, while IL-1 δ functions similarly to other characterized IL-1 family members, namely IL-1 α , as a modulator of a particular IL-1 family member's function, *i.e.*, IL-1 ϵ . Therefore, these references support an additional, disclosed utility for IL-1 δ as a modulator of immune responses, particularly in anti-viral infections.

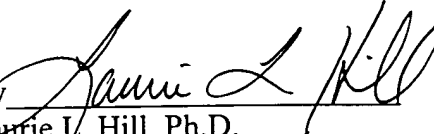
Taken together, the specification discloses IL-1 δ as having a specific, substantial, and credible utility in inflammation, viral infections, and immune responses in general. Therefore, the utility requirement under §§ 101 and 112 has been met. Appellants respectfully submit that the rejections under 35 U.S.C. §§ 101 and 112, first paragraph, are overcome and request the passage of the pending claims to allowance.

IX. CLAIMS INVOLVED IN THE APPEAL

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

Dated: November 26, 2003

Respectfully submitted,

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APPENDIX A**Claims Involved in the Appeal of Application Serial No. 09/770,528**

Claims 1-6 (Canceled)

Claim 7 (Previously presented): A binding compound comprising an antigen binding site from an antibody, which specifically binds to a mature polypeptide comprising at least 8 contiguous amino acid residues from SEQ ID NO:2, wherein said antigen binding site specifically binds an epitope located within said contiguous amino acid residues.

Claim 8 (Previously presented): The binding compound of Claim 7, wherein said binding compound is an Fv, Fab, or Fab2 fragment.

Claim 9 (Original): A kit comprising said binding compound of Claim 7, and:

- a) a compartment comprising said binding compound; and/or
- b) instructions for use or disposal of reagents in said kit.

Claims 10-19 (Canceled)

Claim 20 (Previously presented): A method of:

A) making an antiserum comprising an antibody of Claim 7, comprising immunizing a mammal with an immunogenic amount of a peptide comprising a 12 consecutive amino acid segment of SEQ ID NO:2; thereby causing said antiserum to be produced; or

B) producing an antigen:antibody complex, comprising contacting a rodent IL-1 δ protein or peptide with a binding compound of Claim 7; thereby allowing said complex to form.

Claim 21 (Original): The binding compound of Claim 7, wherein said antibody is a polyclonal antibody.

Claim 22 (Original): The binding compound of Claim 7, wherein said antibody is detectably labeled.

Claim 23 (Original): The binding compound of claim 7, wherein said at least 8 contiguous amino acid residues of SEQ ID NO:2 is selected from the group consisting of residues 8-24; 27-48; 56-73; 77-106; 108-125; 130-156; and 74-98.

Claim 24 (Original): The binding compound of claim 7, wherein said polypeptide comprises at least 12 contiguous amino acid residues from SEQ ID NO:2.

Claim 25 (Previously presented): The binding compound of claim 24, wherein said 12 consecutive amino acid segment is selected from:

- (1) LeuCysPheArgMetLysAspSerAlaLeuLysValLeuTyrLeuHisAsn-Asn;
- (2) IleSerValValProAsnArgAlaLeuAspAlaSerLeuSerProValIle-LeuGlyValGln;
- (3) SerProValIleLeuGlyValGlnGlyGlySerGlnCys;
- (4) ProIleLeuLysLeuFluProValAsnIleMetFluLeu;
- (5) ThrSerSerPheGluSerAlaAlaTyrProGlyTrpPhe;
- (6) PheLeuCysThrSerProLguAlaAspGlnProVal; or
- (7) ThrGlnIleProGluAspProAlaTrpAspAlaProIle.